

Original Article

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TANAFFOS 

Short Term Effects of Tiotropium on COPD Patients Treated with Long Acting Bronchodilators

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Background: The results of bronchodilator therapy in chronic obstructive pulmonary disease (COPD) are not satisfactory and because of this, many drugs are administered for treatment of disease. We examined the short-term additive bronchodilator effects of tiotropium in patients with stable COPD already treated with salmeterol twice daily.

Materials and Methods : in a double-blind, double-dummy randomized study we evaluated the acute bronchodilator efficacy of a single 18 µg dose of tiotropium in patients with COPD under chronic treatment with a long acting beta-adrenergic (salmeterol 50µg twice a day). Measurements of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and six-minute walking test (6 MWT) as indicator of daily activities were made before and after giving the drug. A total of 129 outpatients with stable COPD (Gold level 2 -3- 4) were enrolled and 92 completed the study.

Results: Tiotropium elicited a significantly greater bronchodilation than the placebo. The action of the drug was elicited as increase in FEV1 ($p \leq 0.001$) and FVC ($p \leq 0.001$); 6-MWT increased 35 meters in patients treated with tiotropium compared to 2.5 meters in those receiving placebo ($p \leq 0.001$).

Conclusion: Addition of tiotropium to chronic administration of a beta-adrenergic drug such as salmeterol induced an increase in pulmonary function parameters and in exercise capacity suggesting that association of the two drugs can be more efficient for treatment of disease and improvement of daily living activities than beta-adrenergics alone.

Key words: Chronic obstructive pulmonary disease, Pulmonary function, Six- minute walk test, Tiotropium

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease that can be defined as a pathologic illness characterized by a progressive reduction of respiratory function (1). The flow-limitation of COPD is due to the reduction of the calibre of the respiratory airways caused by the contraction of smooth bronchial muscles and by the reduction of pulmonary elasticity leading to pulmonary hyperinflation (2).

Spirometry; therefore, is the most important test in the diagnosis and staging of COPD. The functional parameters such as forced expiratory volume (FEV 1), forced vital capacity (FVC), slow vital capacity (SVC) and inspiratory capacity (IC) are the simplest parameters to evaluate the gravity of the disease (3). FVC, SVC and IC can provide some indirect information about hyperinflation, a very important indicator of severity of the symptoms and are highly correlated with the degree of dyspnea (4).

Pharmacological therapy can actually reduce dyspnea and improve exercise tolerance (5). In addition to beta-adrenergic drugs, newer anticholinergic drugs have been recently introduced. These drugs block muscarinic receptors for acetylcholine in the airways, and thus produce a reduction in vagal tone (3).

Five subtypes of human muscarinic receptors have been discovered (from M1 to M5), but in the airways only three subtypes appear (M1, M2, M3). M1 and M3 receptors are stimulated by acetylcholine with the cholinergic effect of bronchoconstriction, while M2 receptors inhibit the release of acetylcholine producing an inhibitory feedback on bronchoconstriction (3). Tiotropium is a potent and highly specific competitive antagonist especially for M1 and M3 receptors (6). Based on several studies it appears that in patients with COPD tiotropium can significantly reduce the level of dyspnea (7), improve the quality of life (7), and improve the parameters of hyperinflation such as IC, FRC, RV (8) and exercise tolerance (9). Several short and long term studies on tiotropium have shown an improvement in respiratory function tests greater than with ipratropium (10) or with salmeterol twice daily (11).

Some studies have recently been published, showing the possibility of augmenting the bronchodilator efficacy in patients with COPD by using the combination of tiotropium with a long- acting beta-adrenergic such as salmeterol (12) or formoterol (13,14). The effects observed were faster and greater using the combination of two drugs instead of tiotropium only. We examined the short-term additive bronchodilator effects of tiotropium in patients with stable COPD already treated with salmeterol twice daily.

MATERIALS AND METHODS

a) Aim of the study

This study aimed to determine if a single dose of 18 µg of tiotropium bromide was associated with an improvement in morning lung function and tolerance of daily exercise test. The study took place at the Pulmonary

Rehabilitation Unit of General Hospital of Sestri Levante, Italy from January 2006 to April 2008.

b) Inclusion and exclusion criteria

The study groups consisted of 129 outpatients (79 males, 50 females), with a mean age of 67.3 yrs. and stable COPD. There were 55 level 2 GOLD, 50 level 3 GOLD and 24 level 4 GOLD patients (15). Eligible participants were all adults, had no exacerbation in the last 60 days, had FEV $1 \leq 60\%$ of predicted value, scored between 2 to 4 on the Modified Medical Research Council (MMRC) dyspnea questionnaire, and had been treated with salmeterol alone (50 µg twice a day) for more than three months.

Exclusion criteria were: history of a respiratory allergic disease ; a coexisting cardiovascular or pulmonary disease and/ or an orthopedic or cognitive impairment that prevented them from performing pulmonary function testing, 6-minute walk test (6 MWT) or from completing the questionnaire.

The characteristics and the subdivision of patients are illustrated in Table 1 and the patients' flow-chart in figure 1.

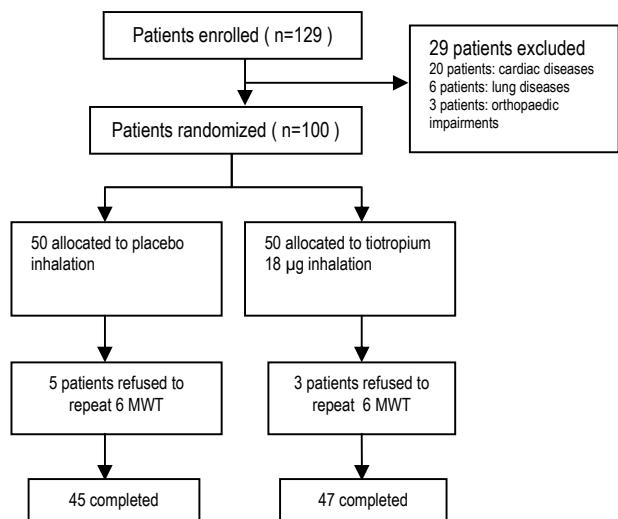
The study was carried out according to the rules of the "Declaration of Helsinki"; the local ethics committee approved our study. All patients provided written informed consent before beginning the study.

Table 1. Enrolled patients' demographics and baseline characteristics

	TIOTROPIUM PATIENTS	PLACEBO PATIENTS
Number of patients	50	50
Average age (yrs.)	69.58±7.81	67.11±5.64
Sex(males %)	70,0%	66,0%
Smokers	29	23
Ex-smokers	21	27
FEV 1 (ml) *	1110±419.0	868±0,72
FEV1% predicted *	55.6±6.82	56.9±7.18
FVC (ml) *	2290±735.7	1926±570.6
FVC% predicted*	64.8±7,96	65.3±6.88
Tiffeneau Index * (T.I.)	51.84±9.56	44.86±8.63
6-Minute Walk Test (meters)	165±65	193±79
MMRC**	3.0±0.8	2.9±0.9
BODE Index	6.27±1.51	6.32±2.39

* Post-bronchodilator value

** Modified Medical Research Council Dyspnea Scale

Figure 1. Patients' flow chart**b) Protocol**

The study was performed using a double-blind, double-dummy randomised design. Patients received a single dose of 18 µg of tiotropium bromide dry powder capsules delivered via the Handihaler or a single dose of placebo delivered via the Handihaler. For allocation of the participants a computer-generated list of random numbers was used. To avoid any bias, single dose of each drug was given to patients by different nurses. The nurses did not know which drug the patient received.

All treatments were administered at the same time (between 8 and 9 a.m.).

Consumption of cola drinks, coffee or tea was avoided 6 hours before administering the drug and during the investigation.

c) Functional measurements

On test day measurements of FVC, FEV1 and Tiffeneau index (T.I.) were recorded one hour before and one hour after administering the drug. Spirometric examinations were conducted three times (according to ERS/ATS standard) (16) and the results of the best FVC and FEV1 of three exams were considered in the subsequent analysis. For the measurements we used Cosmed PFT 4 spirometer (Rome, Italy).

A six minute walk test (according to ATS guidelines) (17) was performed one hour before and one hour after the administration of drug. At the beginning and at the end of each six minute walk test the degree of dyspnea (Borg scale), pulse, respiratory rate and SpO₂ were determined.

d) Statistical analysis

Spirometric data (FVC, FEV1 and TI) and the 6 MWT results were analyzed using the Student's t-test for paired variables. A probability level of $p \leq 0.05$ was considered significant for all tests.

RESULTS

One hundred twenty-nine patients were enrolled and 100 were randomized. Twenty-nine patients were excluded because of concurrent cardiovascular disease. Fifty patients were allocated to inhalation of 18 µg tiotropium bromide and fifty were allocated to inhalation of placebo. Ninety-two patients completed the study. Eight patients refused to repeat the six minute-walk test. The changes in FVC 1 hour after administration of tiotropium were greater than those induced by placebo (an increase of 170 ± 10.76 ml versus no increase induced by placebo) and the difference was statistically significant ($p \leq 0.001$).

Also, the changes in FEV1 1 hour after administering tiotropium were significantly greater than those induced by placebo (an increase of 132 ± 0.430 compared to no increase induced by placebo) ($p \leq 0.001$) (Figure 2 and 3). Tiotropium induced a small improvement in Tiffeneau index greater than placebo, but the difference between the two treatments was not statistically significant ($p \leq 0.148$). The changes in six minute-walk test distance 1 hour after administration of tiotropium were greater than those induced by placebo (an increase of 35.50 meters induced by tiotropium compared with 2,50 meters induced by placebo) and this difference was statistically significant ($p \leq 0.001$, Figure 4).

The average values of FVC, FEV1 and 6 MWT before and after administration of drugs and p-values are reported in table 2.

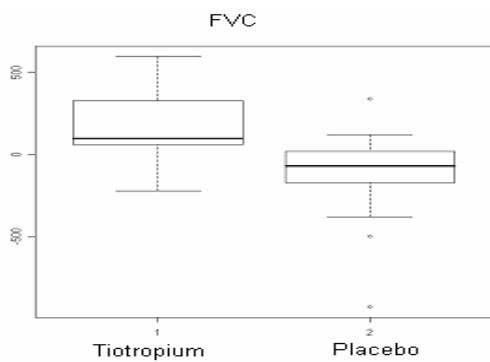


Figure 2. Median changes in FEV1 (ml) before the administration of tiotropium (group 1) and placebo (group 2) and after the administration of tiotropium and placebo ($p < 0.001$)

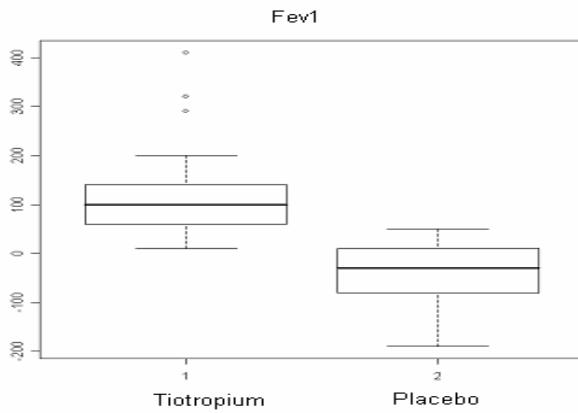


Figure 3. Median changes in FEV1 (ml) before the administration of tiotropium (group 1) and placebo (group 2) and after the administration of tiotropium and placebo ($p < 0.001$).

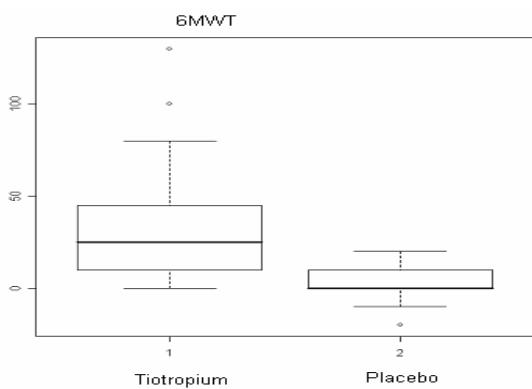


Figure 4. Median changes in 6 MWT (meters) before the administration of tiotropium (group 1) and placebo (group 2) and after the administration of tiotropium and placebo ($p < 0.001$).

Table 2. Changes in FVC, FEV1 and 6 MWT before and 1 hour after the administration of tiotropium or placebo ($p \leq 0.001$)

	Tiotropium	Placebo	
FVC before drug(ml)	2120±627,5	1821±492	
FVC after drug(ml)	2290±735,5	1798±88	
FEV1 before drug(ml)	1110±419	866,5±273,5	
FEV1 after drug (ml)	1232±462	808±308	
6MWT before drug (meters)	320±165	320±193	
6MWT after drug (meters)	350±200	330±196	
Difference after drug	Average	Average	p value
- before drug	Tiotropium	Placebo	(t-student)
FVC (ml)	167.2 ± 197.7	- 106.4 ± 237.5	<0.001
FEV1 (ml)	120.4 ± 96.7	- 42.4 ± 67.2	<0.001
6MWT (meters)	34.7 ± 32.9	2.0 ± 8.6	<0.001

DISCUSSION

Bronchodilation may be achieved either by stimulating adrenergic receptors or by inhibiting muscarinic receptors. These two different mechanisms of action (18), both are associated with improvement of dyspnea, functional parameters, exercise tolerance and quality of life (8,11,15).

A recent paper has revised the idea of reversibility in COPD (19). An average increase in FEV1 after administering a short- acting bronchodilator occurs in the majority of patients, approximately 100- 130 ml and this parameter is smaller than the threshold of 200 ml which is clinically considered significant (19). Like residual functional capacity and inspiratory capacity (8), forced vital capacity can also be an important indicator of bronchodilation. This is a parameter of respiratory function that has not been sufficiently appreciated. The increase of vital capacity indicates a larger moving volume of air and a reduction of air trapping. Thus, a bronchodilator can produce reduction of dyspnea and an improvement in exercise tolerance (20). Another study has shown that therapy with both tiotropium and budesonide/formoterol produces significant improvements in morning lung function, morning symptoms, as well as in patients' ability to perform morning activities. This signifies an improvement in health-related quality of life (21).

Our study aimed to reproduce real- life conditions and was done to determine whether or not a short- term

functional improvement (an increase in patients' ability to perform activities of daily living) obtained by adding tiotropium is superior to the use of salmeterol alone. The obtained results, increased FEV1 (≥ 120 ml) and FVC (≥ 170 ml), demonstrate that an inhalation of a single dose of 18 μ g of tiotropium produces an improvement in expiratory volume and a reduction in hyperinflation (19, 20) over and above that produced by salmeterol alone. In addition, there was a significant improvement in distance covered during the six-minute walk test.

In conclusion, this study demonstrates that adding tiotropium to salmeterol produces not only a greater bronchodilation than placebo in patients previously treated with a beta-adrenergic drug alone, as suggested by previous authors (22-24), but also improves exercise tolerance and the ability to perform morning daily living activities.

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Conflict of Interest

This study was carried out independently from manufacturers and the author has no conflict of interest to declare.

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